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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,401	09/11/2008	C. Frank Bennett	ISPH-0852USA	5614

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
05/02/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/559,401	BENNETT ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26-30,33-42,44 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26-30,33-42,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 12-27-10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 26-30, 33-42, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al (WO 92/03139) and Bennett et al (USPN (USPN 6,077,833) and Pietrzkowski et al (USPN 5,849,903), the combination in view of Wright et al (USPN 5,795,876), Cook et al (USPN 6,440,943) and Wollyniec et al (Am. J. Resp.

Cell & Molec. Biol., Vol. 18, pages 777-785, 1998), the combination further in view of Wang et al (USPN 6,403,566).

Bennett et al (WO 92/03139) teach the antisense oligonucleotide of SEQ ID NO. 22, and antisense which comprise 8-50 nucleobases and comprise SEQ ID NO. 22, which specifically targets and inhibits the expression of ICAM-1 of SEQ ID NO. 138 in humans, and which optionally comprises 2'-O-methoxy modified sugars, phosphorothioate internucleotide linkages (See the entire document, esp. SEQ ID NO. AAQ22650 and the claims).

Bennett et al (USPN 6,077,833) teach the antisense oligonucleotide of SEQ ID NO. 22, and antisense which comprise 8-50 nucleobases and comprise SEQ ID NO. 22, which specifically targets and inhibits the expression of ICAM-1 of SEQ ID NO. 138 in humans, and which optionally comprises 2'-O-methoxyethyl modified sugars, phosphorothioate internucleotide linkages, 5-methyl cytosines, and which optionally comprises 5' wing – gap - 3' wing segments, and which antisense inhibits the expression of ICAM 1, and is optionally co-administered with a steroidal anti-inflammatory agent (see entire document, esp. SEQ ID NO. 17, Fig. 6, paragraphs 14, 24, table 3, 102-106, claims 1-46, esp. claims 14-17, 41 and 43).

Pietrzkowski (USPN 5,849,903) teach the routine administration of antisense to the lungs for inhibition of a target gene in the lungs (see esp. the second paragraph in the section entitled *Pharmaceutical Preparations of Oligonucleotides*).

The primary references do not teach antisense oligonucleotides comprising bicyclic sugars, nor the administration of therapeutic agents to inhibit eosinophil infiltration in the lungs.

Wright et al (USPN 5,795,876) teach the administration of antisense *in vivo* to inhibit eosinophil infiltration and accumulation in the lungs (see esp. paragraphs 173-175, example 19).

Cook et al (USPN 6,440,943) teach the design, synthesis, and use of antisense oligonucleotides for targeting ICAM-1, and therapeutic approaches to treating inflammatory diseases and disorders using these antisense, as well as teaching *in vitro* assays for eosinophil infiltration (see entire document, esp. paragraph 72).

Wollyniec et al (Am. J. Resp. Cell & Molec. Biol., Vol. 18, pages 777-785, 1998) teach reduced inflammation and eosinophilia in ICAM-1 deficient mice, and the relationship between ICAM-1 expression and its essential role in enabling eosinophils to enter the airways of an organism. Wolyniec et al teach ICAM-1 as an important ligand for eosinophil migration into the airways (see entire document, esp. the abstract, introduction on pp. 777-8; p. 780, including Fig. 2; p. 783, including Fig. 6).

Wang et al (USPN 6,403,566) teach the design, synthesis and advantages of incorporating bicyclic sugar modifications into antisense oligonucleotides (see entire text, esp. paragraphs 1-12).

It would have been obvious to utilize the well known antisense oligonucleotide of, and comprising SEQ ID NO. 22 to target ICAM-1, of SEQ ID NO. 138, and inhibit its expression because this inhibition of ICAM1 expression using antisense, including SEQ

ID NO. 22, has been shown by many in the art, including Bennett and Bennett. It would have obvious to utilize the well known delivery devices for efficient lung delivery of the therapeutic antisense because the role of ICAM-1 expression in the lungs for eosinophil migration was well known in the art, as taught previously by Wollyniec, and delivery antisense to the lungs was routine in the art, as illustrated by the teachings of Pietrzkowski. One would have been motivated to use antisense oligonucleotides to inhibit ICAM1 expression to treat eosinophilia because ICAM-1's involvement in inflammation and eosinophilia was well known in the art, as taught previously by Wright, Bennett, Bennett, Cook and Wollyniec. One would have been motivated to combine well known inflammation inhibitors, including steroidal agents, with the antisense to provide treatment effects for inflammation because such combination therapy had been taught previously in the art, as shown by Bennett.

One would also have been motivated to incorporate the many well known modifications, including phosphorothioate internucleotide linkages, 5-methyl cytosines, gapmers, 2'-O- sugar and bicyclic sugar modifications into antisense oligonucleotides because the technology to incorporate these modifications into antisense oligonucleotides was routine in the art at the time of the instant invention, had been taught previously by many in the art, and were well known to impart advantageous properties to antisense, including imparting enhanced stability, target binding and cellular uptake. One of skill in the art would have reasonably expected that SEQ ID NO. 22, and including the modifications claimed, and using the well known lung delivery devices routinely used in the art, would provide for inhibition of ICAM1 expression in

vitro and in the lungs in vivo, and would provide for the treatment effects claimed, including reducing inflammation and reducing eosinophilia and their migration to the lungs, relying on the prior art teachings of Wright, Bennett, Bennett, Cook, Wang, Pietrzkowski and Wollyniec.

For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time of filing.

Response to Arguments

Applicant argues that there is no reasonable expectation of success that compounds targeting ICAM-1 can be successfully administered via the lung or would reduce eosinophil recruitment. Contrary to applicant's argument, ICAM-1 was a known target in inflammatory disorders such as asthma, as evidenced by Bennett et al. (WO). It was routine to deliver antisense oligonucleotides to the lung. Therefore, one would certainly expect a reasonable success of delivering a known antisense oligonucleotide, instant SEQ ID NO: 22 to the lung when the oligonucleotide was known to be an asthma target.

Bennett et al. (WO) teach that it has been hoped that inhibitors of ICAM-1 and VCAM-1 expression would provide a novel therapeutic class of anti-inflammatory agents with activity towards a variety of inflammatory diseases such as asthma (see page 5). Bennett et al. teach that both VCAM-1 and ICAM-1 are inflammatory cell adhesion molecules that can be perturbed in the treatment of diseases with immunological components (see page 6).

The instant oligonucleotide (SEQ ID NO: 22) was known in the art and this specific target was known to be a target in asthma. Therefore, it would certainly be obvious to use routine means to deliver to the lung, such as aerosol and would expect the instantly recited outcome.

Applicant argues the teachings of Wright et al. Wright et al. teach at Example 19 inhibition of VCAM-1. However, the example teaches that ovalbumin-sensitized models are models for respiratory diseases, such as asthma, and this model of pulmonary inflammation involves eosinophilia, as does the asthmatic human. Wright et al. teach that inhibition of VCAM-1 would be expected to inhibit eosinophil accumulation in the BAL fluid.

Given the combined teachings of Bennett et al. (WO) and Wright et al., one would reasonably expect for inhibition of VCAM-1 or ICAM-1, both taught to be asthma targets by Bennett et al. (WO) to have the effects on eosinophil accumulation as taught by Wright et al.

With regards to eosinophil recruitment, Wollyniec et al teach reduced inflammation and eosinophilia in ICAM-1 deficient mice, and the relationship between ICAM-1 expression and its essential role in enabling eosinophils to enter the airways of an organism. Wolyniec et al teach ICAM-1 as an important ligand for eosinophil migration into the airways (see entire document, esp. the abstract, introduction on pp. 777-8; p. 780, including Fig. 2; p. 783, including Fig. 6).

Although ICAM-1 expression conditions may not be identical to the instant specification, as Wolyniec et al. utilize knockout mice, this does not negate the

teachings of Wolyniec et al. with regards to ICAM-1 expression and its essential role in enabling eosinophils to enter the airways of an organism, thereby offering an expectation that delivery to the lung of the specific oligonucleotide of Bennett et al. would in fact reduce eosinophilia.

Applicant argues the interchangeability of different inhibitory molecules. However, this is irrelevant to the instant rejection. The rejection is not based on selection of specific type of inhibitory molecule. The instant oligonucleotide is known in the art and is known to be targeted to ICAM-1, which is a known asthma target. The question is not if the instant compound would inhibit ICAM-1 expression. Additionally, there is teachings in the prior art that would cause one of ordinary skill in the art to expect that inhibition of ICAM-1 in asthma would in fact reduce eosinophilia.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on (571) 272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
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